BINDER
Best conditions for your success

Validation and qualification

in the regulated environment

Content

Introduction

The use of qualified equipment in a regulated industry is an essential part of the quality assurance process; it's also a legal obligation. The below current whitepaper will give an overview on validation and qualification in a GMP environment. It further describes the general approach to qualification with the essential steps DQ1, IQ2, OQ3 and PQ4. The focus is on device qualification. The validation of computerized systems is also discussed.
This whitepaper is addressed to individuals who didn´t come in contact with such topic before.

1 Good Manufacturing Practice, 2 Design Qualification, 3 Installation Qualification, 4 Operational Qualification, 5 Performance Qualification

History

Each medicinal product throughout its whole life cycle under administrative supervision has to guarantee consumer safety. Medicinal products have to be produced to match the specified quality. The first quality assurance system was introduced to the pharmaceutical industry in the 1960s in order to fulfill this regulatory requirement. These quality systems are better known as the Good Practices.

Good Manufacturing Practice (GMP)

For each phase in the life cycle of a drug there are Good Practices to follow: from development & trials to manufacturing and distribution.

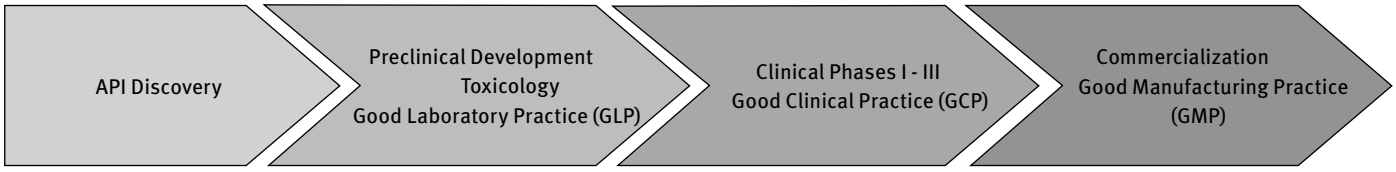


Fig. 1 Life cycle of a medicinal product

The term Good Manufacturing Practice (GMP) was introduced by the Food and Drug Administration (FDA). GMP is a globally recognized governing body, considered as a collection of rules and explanatory guidance's.

The GMP rules had been published by the World Health Organization (WHO) in 1968. With time further Good Practices were introduced to regulate the industry such as, Good Laboratory Practice and Good Clinical Practice.

These Good Practices were supposed to be obligatory for the pharmaceutical industry also in other industry sectors like alimentation and cosmetics which have their Good Practices.

GMP publications of different organizations

Both authorities FDA for the USA and EMA for the European Union which are responsible for the surveillance and regulatory affairs of medicinal products have published GMP rules on a national level. The International Conference on Harmonization (ICH) as well as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) have published GMP guidelines on an International level. The PIC/S is an organization that is meant to improve the co-operation between the regulatory authorities and the pharmaceutical industry.

The ICH is an international organization which support harmonized and mutually accepted GMP rules for the USA, Japan and The European Union.

An overview on GMP and GLP publications are listed in the table below.

Organization	Publication	Title	Content / comment
EMA	GMP	EU Guidelines for good manufacturing Practice for Medicinal Products for Human and Veternary Use Part I - Basic Requirements for Medicinal Products Part II - Basic Requirements for Active Substances used as Starting Materials	GMP requirement for drugs and APIs Validated processes Continous Stability Studies Risk managent
	Annex 11	Computerized Systems	
	Annex 15	Qualification and Validation	
	Annex 20	Quality risk management	
FDA	Title 21 CFR Part 210 Title 21 CFR Part 211	CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS	GMP requirements for drugs and active pharmaceutical substances
	Guidance for Industry	Process Validation: General Principles and Practices Final Guidance for Industry and FDA Staff	
WHO	WHO, Annex 2	Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles	Minimum requirements on GMP, worldwide
ICH	ICH, Q1A	Stability Testing of New Drug Substances and Products	Harmonised guidelines for USA, Japan and EU
	ICH, Q7A	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	
	ICH, Q8A	Pharmceutical Development	
	ICH, Q9A	Quality Risk Management	
PIC/S	PI 006-3	RECOMMENDATIONS ON VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION CLEANING VALIDATION	Guidance
	PS/INF 11/2015	GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEX 15	Identical to Annex 15 of the european GMP

The US American cGMP (current Good Manufacturing Practice) is part of the Code of Federal Regulations 21 CFR 210 (Drugs) and 21 CFR Part 211 for active substances and legally binding for manufacturers and importers. The cGMP undergo strict annual revision.
In the European Union there are also two GMP guidelines, Part 1 addresses to medicinal products manufacturers and Part 2 addresses to the manufacturers of active pharmaceutical substances (API)

The European GMP Part 1 specifies eight chapters of basic requirements on quality assurance and quality control, to the development and manufacturing process, also on the staff, facilities and equipment used. An essential requirement for both parts is the performance & continuous stability studies for pharmaceutical products and active pharmaceutical substances. These stability studies can be conducted in a constant climate chamber of BINDER.

"(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
(ii) Critical steps of manufacturing processes and significant changes to the process are validated;" European GMP Guideline Part 1

Validation

Validation is a method of quality assurance and an important part of the GMP. The European GMP guideline defines validation as the following:

"Action of proving, in accordance with the principles of Good Manufacturing Practice, that any
Procedure, process, equipment, material, or activity. Actually leads to the expected results (see also qualification)."
European GMP Guideline Part 1

The FDA´s definition requires manufacturers a clear understanding of the manufacturing process:
"Process validation:
The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products."
Guidance for Industry: Process Validation: General Principles and Practices, FDA

Both definitions promote the manufacturers understands and controls all quality relevant processes including their risks assessment and is eager to maintain the validated status. Validation is required by GMP guidelines, however what and how to validate, is not explicitly mentioned in detail.
Guidance to validation is given by Annex 15 of the EU GMP guideline. It contains definitions of validation / qualification and further specifies the set-up of a validation, as well as the risk assessment. Annex 20 gives further information on quality risk management which textual which is equal to the ICH Q9 Guideline Quality risk management.

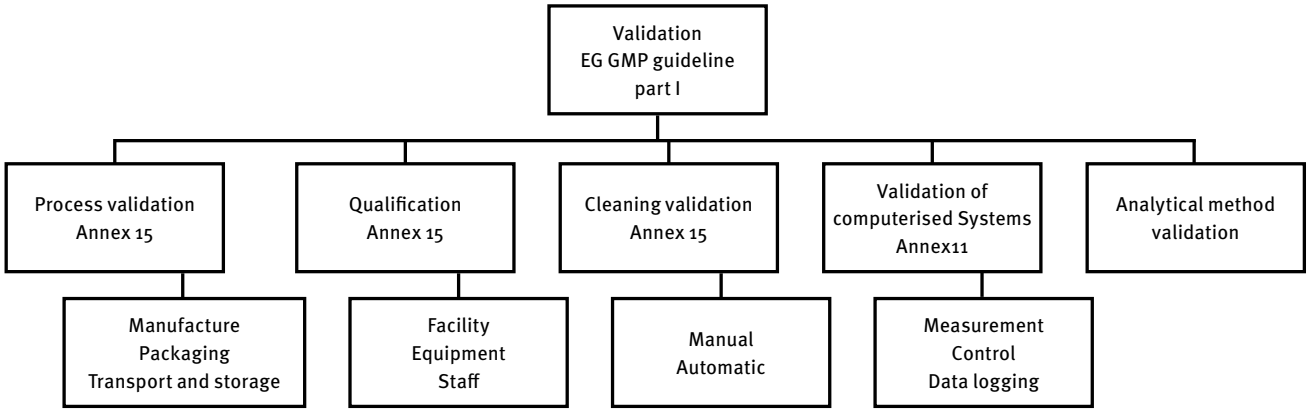


Fig.2 Overview on validation activities

The overview of the validation activities shows that validation is used as the overall term but also describes stand-alone activities like process validation or computer validation. For facilities, equipment and staff the term qualification is exclusively used. There is no official unified terminology but it is generally agreed that qualification refers to everything that is physical and validation refers to methods, procedures and processes. The approach to validation and qualification are the same.

Prior to each validation activity there is a Validation Master Plan (VMP). This governing document contains information about the company, describes the validation project and names the persons in charge. Further it contains the validation policy and states the general approach of how to validate.

The Validation Master Plan includes all validation protocols and validation reports as a requirement of Good Documentation Practice. It is possible to reference existing documents as well as norms and standards.

Types of validation

If possible there should always be a prospective validation performed. This means prior to process implementation. Retrospective validations are used for facilities, when the process is already established using the historical data to provide the necessary documentation to prove that the process is doing what is specified. Concurrent validation is used for establishing documented evidence that processes perform as expected based on information generated while the process is executed.

Qualification

The definition of qualification is an analog to validation:

"Action of proving and documenting that equipment or ancillary systems are properly, installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation."
EU GMP guideline Part 2: Basic Requirements for Active Substances used as Starting Materials

Qualification is a procedure which has four steps:

- Design qualification (DQ)
  The documented verification that the proposed design of the facilities systems and equipment is suitable for the intended purpose.

- Installation Qualification (IQ)
  The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the Manufacturer's recommendations.

- Operational Qualification (OQ)
  The documented verification that the facilities, systems and equipment installed or modified, performs as intended in the specified operating ranges.

- Performance Qualification (PQ)
  The documented verification that systems and Equipment can perform effectively with reproducibility based on the ap proved process Method with the product specification.

› Constant Climate Chamber KBF 1020

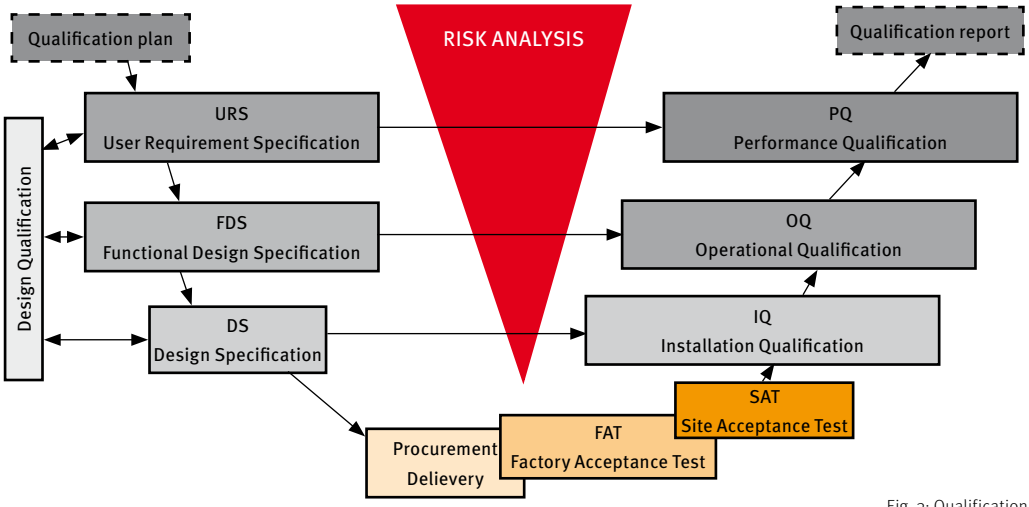


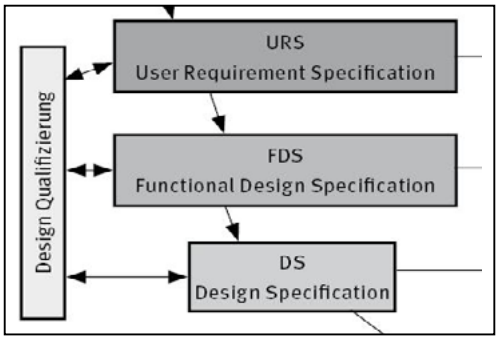
Fig. 3: Qualification schematic

The schematic below illustrates the procedure and how the single elements of the qualification interact with each other:

Prior to all qualification activities a qualification plan has to be set up. It describes all the measures to be executed during the qualification in detail. It defines the responsible persons as well as all tests, further it contains the risk assessment and the acceptance criteria, parameter which are critical to quality and different scenarios of operation. It is common to have the qualification protocol together with the qualification report as one document.

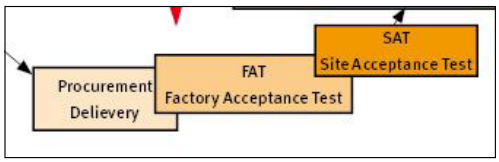
The four phases of a qualification

During the Design Qualification a set of specification documents for the equipment is created:
User Requirement Specification (URS), Functional Design Specification (FDS) and the Design Specification (DS).



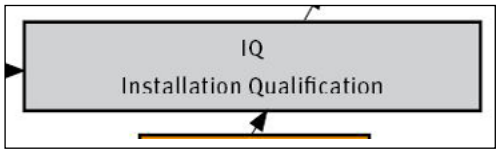
DQ in detail: The user / purchaser describes in the URS the requirements that shall be fulfilled by the piece of equipment. The User requirement Specification also covers the requirements coming from GMP. The URS is the basis for the Performance Qualification. In the next step, based on the URS, the Functional Design Specification is created. The FDS describes the technical functions of the Equipment in detail. The Functional Design Specification is verified by the Operational Qualification. The Functional Design Specification serves for the vendor selection. The next step is the Design Specification which is based on the Functional Design Specification. The DS document contains detailed information including accessories and modifications and documentation. The evidence that the Design Specification is fulfilled, demonstrated and documented by the Installation Specification; for less complex devices like incubators or climate chambers it is possible to create just one specification document. The Design qualification is the most important document because also the qualification protocols and the qualification reports for IQ, OQ and PQ are created. The DQ is completed with the order.

The Factory Acceptance Test (FAT) is performed at the vendor´s site prior to shipping. The FAT returns the documented evidence that the equipment was built according to the specification and functions. The purchaser allows after a successful Factory Acceptance Test the delivery.



The Site Acceptance Test is usually performed at the purchaser´s site to demonstrate that the device functions in between its specification. A FAT and SAT is recommended only for complex devices and / or large projects.

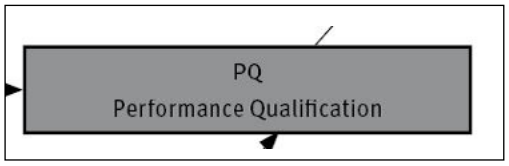
Standard equipment like **climate chambers** or **incubators** rarely have FAT and SAT; normally both tests can be integrated in the Installation Qualification.



The Installation Qualification (IQ) is the documented evidence that the equipment was delivered complete, intact and according to its specification. After a visual examination and checks for missing items the equipment is installed according to the vendors´ documentation. The users will receive an introduction to the equipment. Finally the sensors are calibrated and adjusted.
All performed activities will be documented in a report. This report is the approval for the forthcoming Operational Qualification.

The Operational Qualification OQ) provides the documented evidence that the device works properly in between its specification. E.g. for a climate chamber this means that specified set points for temperature and relative humidity are entered and the actual values are documented in the check list. Further the temperature distribution, the recovery time after a door opening as well as functionality of the temperature alarm can be qualified if this is part of the qualification plan. The chamber remains empty for the Operational Qualification.

During this qualification step the Standard Operating Procedures (SOP) the users have to be available. Further the machine book and a maintenance plan with specifications on maintenance intervals and the scope of the maintenance has to be provided. The Operational Qualification is completed if the qualification protocol is signed by the responsible person. It normal to perform the IQ and OQ validation togeter.



The last qualification activity is **the Performance Qualification (PQ)**. In this step the documented evidence is provided that the device returns the specified results in a reproducible way under manufacturing conditions. The temperature distribution with different loading conditions is of particular interest in case of a climate chamber. Also “worst case” conditions can be part of a Performance Qualification if it’s considered as quality relevant.

The equipment qualification is completed, the final qualification report is approved by the responsible person.

In general a qualification should be performed according to the principle “As much as needed – as little as possible.” in order to remain economic. To reduce the expenses, existing documents can be used.

Especially in the case of standard equipment like constant climate chambers standardized qualification documents created by the vendor can be integrated to their in-house documentation. BINDER offers qualification documents to perform IQ, OQ, PQ which can be adapted to the customer´s specific requirements. These qualification documents describe the methodology and contain check lists and summaries to document each qualification step.

Validation of computerized systems

Computerized systems for measurement, control and data recording are well established in pharmaceutical industry. Annex 11 of the European GMP guideline specifies explicitly that the software should be validated and the IT infrastructure should be qualified as long as the information processing is considered to be relevant for the quality.

In the USA this requirement is also obligatory by Title 21 CFR Part 820. Additionally Part 11 also regulates the use of electronic signatures. There is also a FDA guidance for industry and FDA staff which describes the implementation of Title 21 CFR Part 820.

Climate chambers of BINDER are used for stability studies & can be connected to a corresponding software for control and data logging.

The procedure to validate / qualify an IT system is equal to a validation / qualification of a device or a process.

Validated System

The successful qualification together with the validation of the manufacturing process is the basis to validate the whole process. Validation / qualification are not one-off events. It is necessary to maintain the validated state.

Trends

A new approach in the GMP guidelines in the European Union and in the USA is the requirement that an Ongoing Process Verification in replacement of the re-validation has to be implemented. This shall guarantee to maintain the validated state continuously. The new way transfers the life-cycle approach from the manufacturing process to process validation. The holistic view considers all phases beginning with the specification to decommissioning.

The authorities prefer more and more that Pharmaceutical manufacturers applies to scientific principles instead of following formalisms stubbornly. This means for the device qualification to operational and performance qualifications have to be performed from time to time to maintain the validated state.

Concluding remark

The user in the regulated environment has no alternative to the validation of processes which are quality-relevant. Depending on the complexity of the system there are some efforts to be made to achieve a validated system. A validation can be very cost intensive and also can bind other resources of a company.

The clear requirement, processes have to be planned, specified, analyzed and continuously verified has its advantages: a precise and detailed planning in combination with a risk analysis can also save costs because “surprises” are unlikely to occur during operation. Keeping the specified product quality prevents the manufacturer from expensive product recalls.

Literature

WHO, Annex 2 WHO good manufacturing practices for pharmaceutical products: main principles

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines.
Part I - Basic Requirements for Medicinal Products
Part II - Basic Requirements for Active Substances used as Starting Materials
Annex 11 Computerised Systems (revision January 2011)

Annex 15 Qualification and validation

ICH, Q1A, Stability Testing of New Drug Substances and Products
ICH, Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
ICH, Q8A Pharmaceutical Development
ICH, Q9A Quality Risk Management
ICH, Q10A Pharmaceutical Quality System

FDA, Guidance for Industry: Process Validation: General Principles and Practices
General Principles of Software Validation; Final Guidance for Industry and FDA Staff
FDA, General Principles of Software Validation; Final Guidance for Industry and FDA Staff
PIC/S: GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEX 15 *
PIC/S, PI 006-3:RECOMMENDATIONS ON VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION CLEANING VALIDATION

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About BINDER:
BINDER is the world‘s largest specialist in simulation chambers for the scientific and industrial laboratory. With its technical solutions, the company contributes significantly to improving the health and safety of people. Our range of products is well-suited for routine applications, highly specialized work in research and development, production and quality assurance. With approx. 400 employees worldwide and an export quota of 80%, BINDER 2015 sales were more than 60 million euros.

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